REMARKS

I. Status of the claims

Claims 1-4, 6-15, 17-26, and 28-46 are pending in this application. Claims 5, 16, and 27 have been withdrawn from consideration. Claims 1, 9-15, 17, 18, 21, 22, 25, 26, 28-31, and 33 were amended in order to more clearly define the subject matter of the invention and not to overcome prior art. The scope of the claims was not narrowed by these amendments. No new matter has been added by these amendments.

Support for the amendments to claims 31 and 33 can be found in page 11, lines 16-17 of the specification. Applicants note that the term "traditional lipid complexes" is not indefinite and is defined on page 15, lines 11-17 of the specification.

II. Claim objections

The Office objected to claims 33 and 34 because claim 33 lacked the word "the" before "micellar complex" at line 5. Claim 33 has been amended accordingly. Applicants respectfully request that this objection be withdrawn.

III. Claim rejections under § 112, first paragraph

New matter

The Office rejected claims 35-38 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Office argues that the limitation "wherein said method does not necessarily require the formation of a lipid film comprising the cationic lipid" is not supported by

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Applicants cited passage in the specification (p. 16, lines 2-6, and Figure 1) because the passage does not refer to, or exclude, the formation of a lipid film. Applicants respectfully traverse.

The specification indicates that traditional complexes of cationic amphiphile/PEG derivatives are formed by preparing a lipid film of the cationic amphiphile before hydration of the cationic amphiphile in aqueous media. Specification at p. 15, lines 11-15. In this context, the specification describes the preparation of the micellar complexes of the invention by direct hydration of the cationic amphiphile, without the formation of a lipid film. Specification at p. 16, lines 2-6. These processes are better illustrated in Figure 1, which contrasts the preparation of traditional lipid complexes as shown in Fig. 1A, with the preparation of the micellar complexes of the invention as shown in Fig 1B. Therefore, the specification provides support for a limitation stating that a method of the invention "does not necessarily require the formation of a lipid film comprising the cationic lipid." Accordingly, Applicants respectfully request that this rejection be withdrawn.

Enablement requirement

The Office rejected claims 1-4, 6-15, 17-26, and 28-34 under 35 U.S.C. 112, first paragraph. According to the Office, the specification, while being enabling for micellar complexes and methods of making and using compositions comprising micellar complexes comprising lipid-derivatized PEG wherein the size distribution of all the micellar complexes within a given composition varies by greater than about 20%, does not reasonably provide enablement for methods of making micellar compositions

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comprising lipid-derivatized PEG, wherein the size distribution of all the micellar complexes within the composition is less than or equal to about 20%. Applicants respectfully traverse.

The Office argues that a critical element of the invention is the addition to cationic lipids of a sufficient amount of PEG derivative. The Office admits that "[g]uidance as to what constitutes 'a sufficient amount of PEG derivative' can be found on pages 18, 19, 25, and 38-42 [of the specification, which] describe three techniques for determining whether or not one has succeeded in adding a sufficient amount of PEG derivative." Office Action at p. 5, lines 1-5. Nonetheless, the Office argues that the "specification discloses no example of a sufficient amount of PEG derivative, and provides no guidance as to what quantities of any PEG derivative are sufficient to practice the invention [nor] are any ranges of amounts of PEG derivative suggested." Office Action at p. 5, lines 5-8. Applicants respectfully disagree.

Contrary to the Office's assertion, the specification provides examples of specific ranges for the concentration of PEG derivatives. The specification discloses the preparation of micellar complexes by mixing hydrated solutions of cationic amphiphile and PEG derivative in a ratio of 1:1 (vol:vol), and indicates that an example of a range of concentrations for cationic amphiphiles and PEG derivatives in solution is between 0.25-16 mM. Specification at p. 37, lines 15-18. Further examples with various cationic amphiphiles and PEG derivatives are provided in Figures 2 and 3. For instance, a ratio of 1.5: 0.5: 2 for GL-67: DMPE-PEG5000: pDNA represents a micellar complex lacking a sufficient amount of PEG derivative (Fig 2B), while a ratio of 1.5: 0.75: 2 for the same

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components represents a micellar complex with a sufficient amount of PEG derivative (Fig 2C). See figure captions on page 14 of the specification. Therefore, the specification not only enables the skilled artisan to determine the value of a sufficient amount of PEG derivative to practice the present invention, but also provides specific examples of concentrations that represent a sufficient amount of PEG derivative.

The Office also argues that the specification "fails to discuss the principles which govern the effect of PEG derivatives on micelle size, or to otherwise provide any theoretical framework which could be used by one of skill in the art to determine what amount of a PEG derivative, in combination with a cationic lipid, could be used to practice the claimed invention." Office Action at p. 5, lines 10-13. The Office cites *In re Fisher*, 166 U.S.P.Q. 18 (C.C.P.A. 1970), apparently to indicate that disclosure of known scientific laws would support enablement of some embodiments in cases involving predictable factors. However, as discussed in the previous paragraph, the present specification provides specific examples of a "sufficient amount of PEG derivative." Furthermore, as already admitted by the Office, the specification discloses at least three methods to determine whether or not a micellar complex has been prepared with a sufficient amount of PEG derivative, for example, observation of particulates in the micellar complex suspension, determination of size distribution of the micellar complexes, and determination of electrophoretic migration in agarose gels. Specification at p. 38-40. The Courts have recognized that such experimentation would not be considered undue because sufficient guidance is provided in the specification. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (indicating

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that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.") See also M.P.E.P. § 2164.01 and 2164.01(a). This type of experimentation is not inconsistent with the passage cited by the Office in *In re Fisher*, which merely indicates the relationship between the degree of disclosure present in an application and the scope of enablement.

With respect to the need to disclose the theory on which the present invention is based, the courts have explicitly indicated that an inventor "need not comprehend the scientific principles on which the practical effectiveness of his invention rests." *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 U.S.P.Q. 1137, 1140 (Fed. Cir. 1983).

In light of the foregoing remarks, Applicants submit that the specification enables the skilled artisan to prepare micellar complexes with a sufficient amount of PEG derivative according to the claimed invention. Therefore, Applicants respectfully request that this rejection be withdrawn.

IV. Claim rejections under § 112, second paragraph

The Office rejected claims 1-4, 6-15, 17-26, 28-36, and 39-44 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse.

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The Office rejected claims 1-4, 6-15, 31, 32, 35, 36, 39, 40, 43, and 44 as indefinite because, in the Office's opinion, it is unclear what is intended by the phrase "a sufficient amount of PEG derivative to form micellar lipids". Specifically, the Office argues that it is unclear what is intended by the term "micellar lipids". The Office suggests replacing the term "micellar lipids" with "micelles" or " mixed micelles" because otherwise, in the Office's opinion, the claim could be construed as requiring the synthesis, by addition of a PEG derivative to a lipid mixture, of lipids, capable of forming micelles. Applicants respectfully disagree.

The term "micellar lipid" is defined in the specification as the product formed "by hydrating the cationic lipid and adding the hydrated cationic lipid to the PEG derivative, which has also been hydrated." Specification at p. 16, lines 3-5. Furthermore, the term "micellar lipid" is used consistently throughout the specification with the same meaning. See, e.g., specification at p. 16, lines 4, 17; p.18, lines 16; 21; p. 19, line 1, p 25, line 4; and p. 38, line 10, among others. Therefore the metes and bounds of the claims are better understood when "micellar lipid" is used instead of "micelles" or "mixed micelles". This is also consistent with the axiom that a patentee is free to be his or her own lexicographer. M.P.E.P. § 2173.05(a); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 U.S.P.Q. 303, 315 (Fed. Cir. 1983). Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Office also rejected claims 1-4, 6-15, 17-26, and 28-30 as indefinite because they require a variation in size distribution of less than or equal to about 20%. In the

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Office's view, the claims fail to provide any standard from which to calculate the 20% variation. Applicants respectfully disagree.

Applicants maintain that claims 1-4, 6-15, 17-26, and 28-30 are not indefinite for the reasons of record. See Preliminary Amendment filed on July 13, 2001, at p. 6-7. However, with the sole purpose of expediting prosecution, independent claims 1, 17, and 25 have been amended to explicitly indicate that "the variation in size distribution of said micellar complexes is less than or equal to about 20% of the average micellar complex size." In other words, the size distribution of the micellar complexes of the invention is characterized by a standard deviation that is 20% of the value of the mean (average) micellar complex size. The skilled artisan would recognize that any population of micellar complexes with a size distribution having a standard deviation of less than or equal to about 20% of the average micellar complex size would be within the scope of this limitation. Therefore, by specifying the value of the standard deviation of the size distribution of a population of micellar complexes, the scope of the claims is clearly defined. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Office rejected claims 1-4, 6-15, 17-26, 28-34 as indefinite because they recite "the size distribution" without antecedent basis. The Office argues that environmental characteristics such as salt concentration and temperature affect the size distribution of micelles and in support of this statement, the Office cites the works of Govender *et al.* (J. Contr. Rel. 75(3): 249-258, 2001) and Robson *et al.* (Biochim Biophys. Acta 573:488-500, 1979). In the Office's opinion, because the claims do not

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set forth the conditions under which size distribution should be measured, one of skill in the art cannot know the metes and bounds of the claims. Applicants respectfully disagree.

Size distribution is an inherent characteristic of a population of micellar complexes. Therefore, recitation of "the size distribution" is proper. Furthermore, Applicants fail to understand how the conditions under which the size distribution is measured are relevant in determining the scope of the claim. Applicants claim a method of making micellar complexes, comprising several method steps, wherein the variation in size distribution of said micellar complexes is less than or equal to about 20% of the average micellar complex size. This language appropriately apprises the skilled artisan of the metes and bounds of the claimed invention. Whether a person skilled in the art chooses to alter the conditions under which the size distribution is measured does not affect the definiteness of the claim because as long as the method steps of the claim are followed, and the variation in size distribution of the micellar complexes is less than or equal to about 20% of the average micellar complex size—regardless of the conditions used to measure the size distribution—such action is within the scope of the claim. Measuring the size distribution under different conditions may alter the result of the determination, but the scope of the claim with respect to said size distribution remains the same, i.e., a variation in size distribution of less than or equal to about 20% of the average micellar complex size. Therefore, Applicants submit that the claims do not require the recitation of the conditions under which the size distribution is measured. Accordingly, Applicants respectfully request that this rejection be withdrawn.

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The Office rejected claims 33 and 34 as indefinite because in the Office's view, it is unclear what constitutes "a sufficient amount of a PEG derivative" because the purpose or characteristic for which the PEG must be sufficient is not stated in the claim. Applicants respectfully disagree. However, with the sole purpose of expediting prosecution, Applicants have amended claim 33 to more clearly define the subject matter of the claim. Accordingly, the office's argument is now moot and Applicants respectfully request that this rejection be withdrawn.

The Office rejected claims 41 and 42 as indefinite because in the Office's opinion, it is unclear what is intended by the limitation "preferably". The Office recommends deleting the word "preferably." Applicants respectfully disagree. Applicants respectfully remind the Office that definiteness of a claim language must be analyzed, *inter alia*, in light of the specification. M.P.E.P. § 2173.02. The specification indicates that the micellar complexes of the invention bind preferably to epithelial cells when compared to traditional complexes. See, e.g. Example 3, specifically at p. 45, lines 3-7. In this context, the word preferably is not indefinite and Applicants respectfully request that this rejection be withdrawn.

V. Claim rejections under § 102

The Office rejected claims 9-11, 13, 14, 17-19, 21, 22, 24-29, and 31-42 under 35 U.S.C. § 102(b) as being anticipated by Harris *et al.* (US Patent No. 5,719,131, issued February 17, 1998). The Office also rejected claims 9-14, 17-19, and 21-46 as

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anticipated by Unger under 35 U.S.C. § 102(e) (US Patent No. 6,028,066, filed May 2, 1997). Applicants respectfully traverse these rejections.

In light of the forgoing remarks and the claim amendments made in order to more clearly define the subject matter of the claimed invention, the Office's arguments with respect to claims 9-14, 17-19, 21-34, and 39-42 are now moot and Applicants respectfully request that these rejections be withdrawn.

With respect to claims 35-38, which are drawn to methods of making micellar complexes wherein the method do not necessarily require the formation of a lipid film comprising the cationic lipid, the Office argues that the claims are anticipated by *Harris* and *Unger* because *Harris* and *Unger* teach no such requirement. Applicants respectfully disagree.

Harris specifically discloses preparation of a cationic lipid film as part of the process of making cationic amphiphile/DNA complexes ("a thin film was produced by removing chloroform form the mixture by evaporation under reduced pressure.") *Harris* at col. 36, lines 60-63; see also col. 45, lines 50-53. *Unger* discloses that methods of preparing micelles involve "suspension of the stabilizing material, such as a lipid compound, in an organic solvent, evaporation of the solvent, resuspension in an aqueous medium, sonication and centrifugation." *Unger* at col. 65, lines 1-7. Although *Unger* does not label it as such, evaporation of the organic solvent in which the lipid had been suspended constitutes an embodiment of the formation of a lipid film referred to in claims 35 and 37.

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The Office has provided no evidence that *Harris* or *Unger* prepare micellar complexes in any way that does not require the formation of a lipid film comprising the cationic lipid. Therefore, the Office has not established that *Harris* or *Unger* anticipate claims 35-38. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Applicants note that although the Office rejected claims 43-46 as anticipated by *Unger*, the Office presented absolutely no arguments in support of this rejection. Therefore, the Office has not established that *Unger* anticipate claims 43-46. Accordingly, Applicants respectfully request that this rejection be withdrawn. Applicants reserve the right to respond to arguments against anticipation of claims 43-46 by *Unger* should the Office decide to introduce such arguments in a later Office Action.

VI. Claim rejections under § 103

The Office rejected claims 1, 9, 14, 15, 17, 19, and 20 under 35 U.S.C. § 103(a) as being unpatentable over Harris *et al.* (US Patent No. 5,719,131, issued February 17, 1998).

According to the Office, *Harris* teaches a method of making micellar complexes wherein 64 different cationic lipid suspensions were combined with equal volumes of 64 different DNA solutions. The Office states that although *Harris* does not teach the combination of lipid and DNA in an 8:1 vol:vol ratio, this volume ratio would have been obvious in view of the fact that *Harris* could just as easily have used equimolar solutions of both lipids and DNA and added the appropriate volumes of each to arrive at the

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range of mass concentrations taught by *Harris*. In the Office's view one would have been motivated in this instance to use a ratio of 8:1 vol:vol to achieve a lipid:DNA mass ratio of 8:1. The Office argues that one would have been motivated to achieve this ratio because the concentration of each of these components is a result-effective variable and that the results of a technique using the composition are affected by concentrations of each of these variables, and one of ordinary skill would be motivated to optimize the concentrations of each variable. The Office further states that in this case, the specification and claims disclose that ratios of 1:1 and 8:1 will yield the claimed compositions, and therefore, in the Office's opinion, the claimed ratio of 8:1 does not appear to be absolutely required for the function of the invention. Finally, the Office indicates that *Harris* teaches ratios covering the range of ratios disclosed as functional by Applicant and that discovering the optimum or workable ranges by routine experimentation would not be inventive. Applicants respectfully traverse this rejection.

The totality of the Office's arguments in this rejection seem to be directed towards proving only that claims 4 and 20 would be obvious over *Harris*. However, the Office did not address the issue of how independent claims 1 and 17, from which claims 4 and 20 depend, would be obvious to the skilled artisan in light of *Harris*. For example, the Office has provided no reasoning supporting, or even suggesting, that the limitation in claims 1 and 17 wherein the variation in size distribution of the micellar complexes of the invention is less than or equal to about 20% would be obvious to the skilled artisan based on *Harris*. Therefore, the Office has not established that claims 1, 9, 14, 15, 17,

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19, and 20 are *prima facie* obvious in view of *Harris*. Accordingly, Applicants respectfully request that this rejection be withdrawn.

VII. Information Disclosure Statement

Applicants filed an Information Disclosure Statement (IDS) on January 6, 2000. However, the corresponding PTO-1449 forms that Applicants received were only partially initialed. The Office only initialed the journal articles cited in the IDS, but not the U.S. and Foreign patents. Accordingly, Applicants respectfully request that the Office initial and return to Applicants the aforementioned PTO-1449 forms, indicating that the Office had considered the references listed therein. For the Office's convenience, Applicants enclose copies of the PTO-1449 forms as-filed.

Conclusion

Please grant any extensions of time required to enter this Preliminary Amendment and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: February 25, 2002

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APPENDIX TO AMENDMENT OF FEBRUARY 25, 2002

Amendments to the Claims

1. A method of making micellar complexes comprising:
   a) combining at least one cationic lipid with a sufficient amount of PEG derivative to produce micellar lipids;
   b) combining said micellar lipids and at least one biologically active molecule to form said micellar complexes,
   wherein the variation in size distribution of said micellar complexes is less than or equal to about 20% of the average micellar complex size.

9. A composition comprising at least two micellar complexes produced according to claim 1.

10. A composition comprising at least two micellar complexes produced according to claim 2.

11. A composition ~~micellar complex~~ according to claim 9, wherein ~~said~~ at least one micellar complex further comprises an agent for targeting a mammalian cell.

12. A composition ~~micellar complex~~ according to claim 11, wherein said agent for targeting is selected from peptides containing a RGD, UDP/UTP, lactose, cyclic RGD peptide, penetratin, lectins, agents to target the LDL receptor, mannose-6-phosphate, HAV peptides, CNP-22 peptides and airway specific single chain antibodies.

13. A composition ~~micellar complex~~ according to claim 9, wherein at least one ~~said~~ micellar complex further comprises a hydrophobic species to coat said micellar complex.

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14. A composition ~~micellar complex~~ according to claim 9, wherein said biologically active molecule is DNA.

15. A composition ~~micellar complex~~ according to claim 14, wherein said at least one cationic lipid and said DNA are present in a lipid:DNA ratio of 1:8 vol:vol.

17. A method of delivering a biologically active molecule to a cell of a mammal comprising contacting said cell with a composition comprising ~~a~~ at least two micellar complexes, wherein ~~said~~ each micellar complex comprises:
at least one cationic lipid;
at least one biologically active molecule; and
a least one PEG derivative
and wherein ~~said~~ each micellar complex in the composition is part of a group of micellar complexes having a variation in size distribution of less than or equal to about 20% of the average micellar complex size.

18. A method of delivering a biologically active molecule to a cell of a mammal according to claim 17, wherein ~~said~~ at least one micellar complex further comprises a co-lipid.

21. A method of delivering a biologically active molecule to a cell of a mammal according to claim 17, wherein at least one ~~said~~ micellar complex further comprises a hydrophobic species to coat said at least one micellar complex.

22. A method of delivering a biologically active molecule to a cell of a mammal according to claim 17, wherein at least one ~~said~~ micellar complex further comprises an agent for targeting a mammalian cell.

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25. A composition comprising at least two micellar complexes, wherein each micellar complex comprises ~~comprising~~:

at least one cationic lipid:

at least one PEG derivative; and

at least one biologically active molecule; and

wherein ~~the variation in size distribution of a group of said micellar complexes is of less than or equal to about 20%.~~ each micellar complex in the composition is part of a group of micellar complexes having a variation in size distribution of less than or equal to about 20% of the average micellar complex size.

26. A composition~~micellar complex~~ according to claim 25, wherein at least one ~~said~~ micellar complex further comprises a co-lipid.

28. A composition~~micellar complex~~ according to claim 25, wherein said biologically active molecule is DNA.

29. A composition~~micellar complex~~ according to claim 25, wherein at least one ~~said~~ micellar complex further comprises an agent for targeting a mammalian cell.

30. A composition~~micellar complex~~ according to claim 29, wherein said agent for targeting is selected from peptides containing a RGD sequence, UDP/UTP, lactose, cyclic RGD peptide, penetratin, lectins, agents to target the LDL receptor, mannose-6-phosphate, HAV peptides, CNP-22 peptides and airway specific single chain antibodies.

31. A method of making micellar complexes comprising:

a) combining at least one cationic lipid with a sufficient amount of PEG derivative to produce micellar lipids;

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b) combining said micellar lipids and at least one biologically active molecule to form said micellar complexes,

wherein the size distribution of said micellar complexes is narrower than the size distribution of traditional lipid complexes ~~prepared without a sufficient amount of the PEG derivative~~.

33. A micellar complex comprising:

at least one cationic lipid;

at least one PEG derivative; and

at least one biologically active molecule;

wherein the micellar complex is part of a group of micellar complexes having a size distribution narrower than the size distribution of traditional lipid complexes ~~prepared without a sufficient amount of the PEG derivative~~.

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